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Hereditary Spherocytosis, Thrombocytosis, and Chronic Pulmonary Emboli: A Case Report and Review of the Literature

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Thrombocytosis in post-splenectomy patients with hereditary spherocytosis (HS) is usually not attended by an increased risk of thrombosis. Review of the literature revealed HS in association with pulmonary thrombosis, portal vein thrombosis, and cerebral infarction in two brothers, TTP in an asplenic patient and a patient with corpora cavernosum thrombosis causing segmental priapism. We report a case of a 30-year-old white male with HS who presented with hemoptysis 29 years after splenectomy. Work-up revealed a hypercoagulable state with thrombocytosis and recurrent pulmonary emboli resulting in severe pulmonary hypertension, cor pulmonale, atrial flutter, and syncope. Am. J. Hematol. 57:82–84, 1998. © 1998 Wiley-Liss, Inc.

Key words: spherocytosis; pulmonary hypertension; pulmonary emboli; thrombocytosis

INTRODUCTION

Hereditary spherocytosis (HS) is an uncommon hemolytic disorder usually not associated with thrombotic risk. The molecular basis of HS is heterogeneous, with the primary defect involving the red cell membrane, resulting in decreased red cell deformability and a predisposition to splenic trapping. Complications associated with HS included gallstones, aplastic crises, leg ulcers, extramedullary hematopoiesis, and hemochromatosis [1]. However, rare cases of both arterial and venous thrombosis have also been described [2–5]. We report the clinical, morphological, and laboratory features of a patient with HS and recurrent venous thromboembolic episodes. This association, to the best of our knowledge, has not previously been described in detail.

CASE REPORT

This 30-year-old white male presented with dizziness, light-headedness, and hemoptysis. He had a history of severe HS with life-threatening hemolysis and had an uncomplicated splenectomy at 9 months of age. Six weeks prior to this admission he developed a dry, nonproductive cough and received oral antibiotics for a presumed bronchial infection. One week prior to admission he experienced non-radiating exertional chest pain, which was relieved by rest. The past medical history was remarkable only for asthma. He is a non-smoker, does not use alcohol or drugs, and at the time of admission was pain-free.

Physical examination showed scleral icterus. There was no evidence of petechiae, bruising, or bleeding, and no calf tenderness or swelling. With the exception of a slight increase in P_2 and a splenectomy scar, the rest of the examination was normal.

Laboratory values included: WBC 21.6 × 10^9/L, hemoglobin 15.8 g/dl, platelet count 769 × 10^9/L, MCV 71.5 fl., MCHC 39.2 g/dl, and the RDW 28.0%. The corrected reticulocyte count was 9.9. Review of the peripheral smear showed 3+ anisocytosis, 2+ spherocytosis, 1+ acanthocytosis, 1+ polychromasia, macrocytosis, and occasional Howell-Jolly bodies. The white blood cell and platelet morphology were normal. Arterial blood gas sampling revealed a pH of 7.43, pCO_2 31 mm HG, pO_2 56 mm HG, HCO_2 21 mmol/L with an A-a gradient of 56.8. Pulse oximetry revealed an O_2 saturation of 88%.

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The LDH was 1,485 IU/L, the Alkaline phosphatase 126 IU/L, and the GGT 203 IU/L. The AST, ALT, and creatinine kinase were all normal. The haptoglobin was <5. The total bilirubin was 3.3 mg/ml, with a direct bilirubin of 0.4 mg/ml (0–0.3). Examination of the bone marrow revealed erythroid hyperplasia and fibrosis, normal maturation of all cellular lines, and complete absence of iron. Immunophenotyping and cytogenetic analysis of the marrow were normal. Direct and indirect Coombs tests were normal. Acid hemolysis and Sucrose lysis tests were negative. Red blood cell pyruvate kinase and G6PD activities were normal. The leukocyte alkaline phosphatase level was 68 U (normal range 89–135). The patient's osmotic fragility was increased; the father's osmotic fragility test was normal. Analysis of red cell membrane protein by Gradient Fairbanks Gel showed a marked decrease in the spectrin-to-band 3 ratio, indicative of severe spectrin deficiency (Sp/B3 = 0.56, control = 0.95 N = 0.97 ± 0.10). Kaolin clotting time was 34 sec (<101), dilute Russell's Viper Venom time was 44 sec (<51), IgG and IgM anticardiolipin antibodies and antinuclear antibodies were not detected. Protein C antigen was 66% (75–120%) and Protein S antigen was 59% (80–120). Antithrombin III levels, fibrinogen, and D-dimers were normal. Platelet aggregation studies with collagen, ADP, epinephrine, arachidonic acid, and ristocetin were normal.

A liver spleen scan did not demonstrate an accessory spleen. The EKG was unremarkable. A chest X-ray showed bulging of the main pulmonary artery with a rounded appearance of the right pulmonary artery. The V/Q scan was interpreted as high probability for pulmonary embolism. Pulmonary angiography was diagnostic of acute pulmonary emboli to the posterior segmental artery of the right upper lobe and a branch of the superior segmental artery of the right lower lobe. Venous doppler of the lower extremities were negative. The patient was then started on heparin. Blood samples were obtained prior to the start of heparin therapy.

One week after admission, the patient remained hypoxic. Pulmonary function evaluations revealed a vital capacity of 4.44 liters (78% predicted), FEV 13.1 liters (67% of predicted) FEV-1/FVC ratio was 70, forced midexpiratory flow was 1.92 liters (35% predicted), total lung capacity 84% of predicted, and DLco 25.79 liters (66% predicted). There was no response to bronchodilators. Surface cardiac echocardiography showed severe pulmonary hypertension. A bubble study did not support a diagnosis of ASD.

After adequate anticoagulation and iron replacement the patient continued to have recurrent dyspnea. The thrombocytosis persisted. Since he was unable to tolerate aspirin, he received hydroxyurea. In spite of these efforts the patient remained hypoxic with V/Q scan evidence of recurrent emboli. A Greenfield filter was successfully placed but subsequent pulmonary angiography showed additional pulmonary emboli to both the right and left lung. An echocardiogram done 1 year after presentation showed an ejection fraction of 70%, severe pulmonary hypertension, 3–4 + tricuspid regurgitation, and a severely enlarged, hypokinetic right ventricle and a small left ventricular cavity. The patient subsequently developed atrial flutter and syncope. He is presently being evaluated for a bone marrow transplant in preparation for a combined heart and lung transplant.

DISCUSSION

There have been seven previous reports of patients with hereditary spherocytosis who have suffered from otherwise unexplained thrombotic events. The first English language report was of a 39-year-old man who had undergone an uneventful cholecystectomy and splenectomy 8 years prior to developing hematemesis. At endoscopy he had large esophagogastric varices. Hepatic arteriography with venous phase study of the portal system showed that the portal and superior mesenteric veins were absent and many large collateral vessels were present. The authors commented that variceal bleeding should be included in the differential diagnosis of post-splenectomy patients with gastrointestinal bleeding and a history of hematological or myeloproliferative disease, but did not speculate on a possible association with HS. This patient did not have an evaluation of his underlying HS nor for a hypercoagulable state (HCS) [2]. The second case, reported in 1988, was of a 19-year-old male with previously documented HS who presented with a lethal episode of refractory thrombotic thrombocytopenic purpura (TTP) who developed exceedingly high reticulocyte counts and LDH levels accompanied by overwhelming hemolysis. Although the clinical presentation and post-mortem results were consistent with TTP, there was no coagulation evaluation described. The authors speculated that the unusual degree of hemolysis was most likely associated with the patient's underlying HS [3]. The third case, also described in 1988, was of a 24-year-old male with previously diagnosed thrombosis of the corpus cavernosum. The authors did not associate this event with the patient's underlying hematological disorder and there was no further hematological evaluation done [4]. In 1989, the cases of two elderly brothers with HS who suffered similar large vessel stroke syndromes were reported. In both cases, there were significant risk factors for cardiovascular disease. Rheological studies performed after each episode demonstrated blood viscosity to be significantly elevated at high shear rates, increased red cell aggregability, and decreased red cell deformability at times when the plasma fibrinogen levels were normal. Further blood clotting studies or evaluation of their HS were not reported. The authors drew attention

to the lack of other reports of HS patients with large vessel strokes and pointed out that rheological abnormalities should predispose to small vessel occlusion due to sludging [5]. A third case of HS with stroke was reported in the French pediatric literature. In 1991 a 59-year-old man with HS and primary pulmonary hypertension was reported. This individual suffered from progressive dyspnea on exertion for 4 months prior to definitive diagnosis. A lung perfusion scan showed nonhomogeneous perfusion that was not consistent with pulmonary embolism. Pulmonary angiography showed diminished peripheral vascular filling with signs of pulmonary embolism. There was no evidence of lower extremity thrombosis on phlebography. A lung biopsy showed fibromuscular hyperplasia of the small- and medium-sized arteries, their lumens occluded by old organized and recanalized thrombi. The authors suggest that the occurrence of this patient's pulmonary hypertension was due to the lack of deformability of his spherocytes and in this regard is analogous to the pulmonary hypertension sometimes seen in sickle cell hemoglobinopathies [6].

The patient reported here presented at a young age with a HCS, thrombocytosis, and recurrent thromboembolic episodes. The bone marrow biopsy was hypercellular and fibrotic, features not typically seen in either reactive thrombocytosis or HS [7], but that are suggestive of bone marrow injury or a myeloproliferative process [8]. Although bone marrow karyotypic analysis, immunophenotyping, and platelet aggregation studies were normal, a myeloproliferative disorder cannot be excluded. The marrow fibrosis, the slightly decreased leukocyte alkaline phosphatase, and the thrombocytosis (which appears elevated beyond what is usually seen post-splenectomy) all support this latter interpretation. That this patient had HS is beyond doubt, as demonstrated by the abnormal osmotic fragility and spectrin analysis.

While thrombocytosis is expected in the post-splenectomy setting, it is not usually associated with thrombotic episodes. However, in this case the combination of hemolysis, thrombocytosis, and HS may have led to a HCS. Previous investigators have established that in the absence of endothelial damage, erythrocytes and endothelial cells do not present sufficient amounts of phosphatidylserine on the cell surface to bind factors X and Xa [9]. In vitro, it has been shown that HS cells have accelerated lipid loss [10], which may provide increased substrate for procoagulant activation. Furthermore, when platelets are activated their phosphatidylserine content increases from 13% to approximately 30% [11]. Platelet activation causes the transfer of anionic phospholipid (primarily phosphatidylserine) from the inner to the outer leaflet of the membrane, accelerating the coagulation process [12,13].

The precise mechanism underlying this patient's hypercoagulable state remains undefined. While release of tissue phospholipids during breakdown of HS cells could result in platelet activation, this process has not been demonstrated in vivo. Alternatively, the patient could have a coincidental myeloproliferative disorder (essential thrombocythemia), although this diagnosis is elusive, and he has no documented platelet dysfunction. Hopefully, empiric correction of his underlying bone marrow disorder will allow him to proceed safely to heart-lung transplant.

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